Visit to IARC, Lyons

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1. Introduction

I invited myself to IARC mainly to discuss their ongoing lung cancer/ETS multicentre case-control study and to compare views on the evidence relating to ETS. I spent some four hours meeting with Dr P Boffetta (PB) and Dr R Saracci (RS) from IARC, and Drs J Tredaniel (JT), recently of IARC, and S Benhamou (SB). JT and SB are based in Paris and are collaborators in the multicentre study. (JT and I will both be speaking on ETS and lung cancer at a meeting in Dijon in July 1994). I also briefly met Dr F X Bosch (FB), recently of IARC, now based in Barcelona, who has been conducting work on black and blond tobacco and on cervix cancer. Unfortunately Dr E Riboli (ER) was unable to be present. Attached to this note are copies of five documents I was given.

ANNEX A: A recently published review of ETS and cancer in adults by JT, PB, RS and A Hirsch.

ANNEX B: A one-year old IARC report on tobacco and cancer which contains inter alia some information on the multicentre study; see particularly the table on p22.

ANNEX C: An older IARC report on health effects of passive smoking in Europe which includes inter alia various sections of the questionnaire used in the multicentre study; on occasional smoking and ETS exposure; on residential history; on medical

data relating to the lung cancer cases; on employment; and on validation of smoking habits.

ANNEXES D and E: Two recently published papers on cervix cancer.

In this note I will for convenience deal briefly first with matters other than ETS and lung cancer, then deal first with the multicentre study and second with interpretation of the overall evidence.

2. Various topics

2.1 International Smoking Statistics

PB had phoned me the day before the meeting asking if I could supply him with data on smoking prevalence in various European countries. I took over my copy of "International Smoking Statistics" by Nicolaides, Wald, Forey and myself which Oxford University Press had sent to me only two days earlier! PB was very interested to see this, as were NB and FB.

2.2 ETS and cancer of sites other than the lung

PB and I agreed that there was little convincing evidence of an effect here. His interpretation of the data, in Annex A, is similar to mine in my Karger book.

2.3 ETS and heart disease

There was some discussion on this. It seemed that Wald and Samet had been influential here in ensuring that official reports, including EPA, had not cited heart disease as being caused by ETS exposure. They felt that the associations in epidemiological studies emphasized by Wells and by Glantz and Parmley could well be due to confounding. The associations were in any case implausibly large vis-à-vis the association with active smoking. I commented on the fact that the American Cancer Society (ACS) had never published their findings for heart disease for either of their million-plus person studies (indeed they have not published any results for the second study in relation to ETS). PB, who worked for a period at the ACS, said that the ACS chief in Atlanta, Clark Heath, saw ETS

as being of low priority and was loth to release their data. However he was only involved in the second study data and Garfinkel apparently was still working on the first study. (The whole thing seems to me a major scandal - they have massive data out there and Garfinkel told me years ago that he had looked and found no association of ETS and heart disease - but how to get the finding published!!)

2.4 Smoking and cervix cancer

Annexes D and E show that human papilloma virus (HPV) is a major risk factor for lung cancer, and that when this is taken into account any effects of smoking are marginal or non existent. I mentioned to EB the study of Slattery on ETS and cervix cancer. He effectively said that because HPV had not been determined it was uninterpretable. Only studies which had first determined the presence of HPV could be used to look at the potential role of other factors. Other studies, he opined, were of an "earlier era" and could be discounted!

2.5 Accuracy of diagnosis of cancer

ER and RS had been involved in study of the accuracy of diagnosis of cancer, including work in Trieste which, like Hungary and Austria, routinely conducts autopsies in patients dying in hospital. However, since the publication in 1991 of IARC Scientific Publication No 112, "Autopsy in Epidemiology and Medical Research", there had apparently been no further work carried out. I did not mention the work PJCR and I had been involved in in Budapest.

2.6 Molecular chemistry

It should be noted that IARC are doing a whole range of studies on various biochemical markers of exposure. See in particular Annex B, pp5-17.

2.7 Studies of tobacco and cancer in developing countries

There have been predictions of large numbers of tobacco related deaths in third world countries in the 21st century, but there is in fact little reliable information on prevalence of smoking or of smoking related disease in many of the countries involved. Annex B describes plans to determine prevalence of tobacco use in India and in Africa, and gives some results from a pilot study in Bombay. It is interesting to note that prevalence is very high in both sexes, with 78.7% of men and 63.2% of women present or past users of tobacco (mainly present). In women nearly all use is smokeless, chewed or applied, but in men almost half the users smoke. This was not discussed at the meeting.

2.8 Black and blond tobacco

FB was involved in reviews of the evidence for a number of smoking related cancers. Generally risks were higher for black tobacco than for blond tobacco, particularly for larynx cancer.

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3. ETS and lung cancer

3.1 The IARC ETS/lung cancer multicentre case-control study

Points to note about this study are as follows:

(i) The objective is to determine if there is a risk of ETS and if so to estimate its magnitude. (Although the IARC Monograph on tobacco smoking considered there is a risk, a view supported in Annex A.)

(ii) There are a total of 11 centres in eight European studies. An Indian centre in Chandrhigar is collecting data on similar lines but its data will probably not be included in what is essentially an EEC project. A Canadian centre was planned at one stage, but has gone its own way.

(iii) Collection of data started between 1989 and 1991 in the various centres. Although some studies will go on collecting data in 1994 and 1995, the analyses in relation to the main objectives will be based on data collected up to the end of 1993, with an expected total (over the two sexes) of 750 lifelong nonsmokers with lung cancer. (The Vienna part may not be included as it found virtually no nonsmokers with lung cancer.) The present expected timing is as follows: cleaning up data ready for analysis first half of 1994; analysis second half of 1994 and first part of 1995); agreeing publications with all the collaborators (traditionally a slow and painful process in IARC) some further months (or years!?); first publication 1996?! I imagine there will be a report to the EEC, who sponsored the work, somewhat earlier than this but not much.

(iv) Histological confirmation of the cases is not a firm requirement but will be achieved in many. There is no formal panel review of slides. Analyses restricted to confirmed cases will be included.

(v) Controls are a mixture of population and hospital controls. Some centres have both types, some only one. Individual matching of cases and controls on sex, age (and in some cases also residential area, race or date of diagnosis) is also carried out in most of the studies.

(vi) Some centres collect data on smoking as well as nonsmoking subjects to look at risk by various aspects of the smoking habit.

(vii) The questionnaire on ETS exposure is standard for the different centres and is very detailed.

(viii) The range of confounding factors studied varies from centre to centre. Most look at occupation, about half look at diet, two look at family history of lung cancer, and one at diesel. Three studies look at radon. One of these is the study by Sarah Darby of the Doll/Peto group in Oxford. In fact radon is the major objective here, and they are also studying pet birds and diet in extenso. (I saw their questionnaire some years ago.)

(ix) Smoking habits of controls but not cases will be validated by urinary cotinine (measured at the American Health Foundation, New York) in some studies. It was not considered useful to validate cases' smoking habits in this way as many lung cancer patients give up because of symptoms

or are not allowed to smoke in hospital. However, for both cases and controls, smoking habits will also be validated in most studies by interviewing the spouse or other next-of-kin. The next-of-kin will also answer questions about his or her own smoking habits, which will allow partial validation of statements made by the subject relevant to ETS exposure.

(x) Samples of blood and oral mucosa will also be taken in most of the centres (from nonsmoking cases and controls and from smoking cases) with a view to investigation of various genetic susceptibility markers such as AHH, P450, debrisoquine and glutathione. Here sampling will continue until the end of 1995 and publication of results is a long way off. It is envisaged the stored samples may be used in the future for some genetic markers not even thought of yet.

Generally, the study will be quite a powerful one and should allow the effect of a number of confounders and of potential sources of bias to be investigated. It will clearly be one of the best, if not the best, of the case-control studies on the issue. However it will, nevertheless, be subject to some of the general weaknesses of such studies, e.g. the problem of recall bias in case-control studies and the problem of accurate quantification of ETS exposure. It is also limited by not including subjects from Japan, Hong Kong and China, areas which have provided much of the data in the past.

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4. Evidence on ETS and lung cancer

I had previously sent to PB a number of copies of my presentation on ETS in Tokyo, published as a book by Karger. I also took my slides from the talk and went through them as a focal point for discussion. Most of the comments made were by PB and RS. There was no animosity, discussion being purely on a scientific basis. Points noted included the following:

4.1 Dosimetry

RS thought the whole argument about whether thresholds existed or did not exist was unproductive. His views seemed to align with mine that one's position on the issue is determined more by faith than by scientific principles. Nevertheless I think that RS believed that it seemed likely, based on active smoking risks and similarity of ETS and MS smoke constituents, that there was some risk.

He noted that a few years ago a small workshop had been convened consisting of Trichopoulos, Geoffrey Rose (who has died recently), Martin Jarvis, Catherine Hill, and himself. This concluded that there were likely to be several hundred deaths a year in the EEC due to ETS. Since the EEC population exceeds that of the US, this is probably about an order of magnitude less than the EPA 3000 deaths figure. The conclusions of the workshop were never published, but RS said he would send me a report on it.

RS said that IARC's function at present was merely to identify hazards and they did not make quantitative risk assessments. However, this may change in the future.

I commented that if the dosimetry implied an effect, then the point could have been made years ago, but e.g. the 1979 Surgeon-General report had not done so. RS noted that someone in 1932 had stated an effect of ETS on lung cancer risk was likely. He would send me the paper if he could find it.

4.2 Lack of evidence for workplace/childhood exposure

The general impression I got was that IARC, unlike me, were not critical of EPA for concentrating on the one index (spousal exposure) for which an association was evident at the expense of other indices (workplace/childhood exposure) for which no association was evident. They felt that marriage to a smoker was a better marker of exposure to ETS than other markers (though they noted that working with a smoker was the next best marker according to the IARC multicentre cotinine study, published by Riboli et al in 1990).

4.3 Histological type of lung cancer

I criticized EPA's failure to present results by histological type, pointing out that some studies claimed an association with squamous cell cancer and not adenocarcinoma, and some the reverse. PB thought the whole issue of histological type in relation to smoking, with adenocarcinoma increasing over time relative to

squamous both in terms of total deaths and its association with smoking, deserved careful review and much more thinking about. I do not disagree with this.

4.4 Publication bias

PB thought this was unimportant. There was so much interest in ETS these days that virtually all data would come out. I had of course not claimed any bias would be substantial.

4.5 Dose-response

PB thought this the strongest part of the evidence against ETS. I pointed out that there were various biases that could artificially produce a dose-response. Though he accepted that misclassification of smoking habits and confounding might do so, he did not think that selection bias (only studies which show an association tend to publish results; studies may choose the index to maximize the dose-response) was material, though it was unclear why not.

4.6 Study weaknesses

I pointed out that studies with apparent design weaknesses tended to produce markedly higher relative risks than those that did not. PB and SB, while accepting that there was an element of validity to this argument, noted that some weaknesses were potentially more serious than others. It may be useful to do further work here isolating weaknesses according to importance.

In some studies one might be able to get internal evidence concerning relevance of some of these biassing factors (e.g. comparing results supplied by the subject and by the next-of-kin). PB suggested it would be interesting to carry out a full and formal meta-analysis in which the raw data were obtained from all the authors so that overall estimates of the magnitude of differences in relative risk according to various features of the studies could be obtained. Although I showed great enthusiasm about this idea, PB thought that in practice it would be difficult to organize until after the multicentre study had been dealt with.

4.7 Confounding by other risk factors

The general impression I got was that PB and RS thought confounding and misclassification of active smoking status were the biasing factors most likely to be of any practical importance. Among the confounders, diet was clearly thought to be the most important candidate to cause bias. I imagine they will not come to any firm views here until they have looked at the data from the multicentre study.

4.8 Misclassification of smoking habits

I mentioned briefly the results from the Japanese spousal study. PB and RS clearly found the very high misclassification rates hard to accept. They also found it remarkable that the cotinine levels were no higher in this study in nonsmokers married

to a smoker than in nonsmokers married to a nonsmoker. They felt the results conflicted with those of the IARC multicentre case control study.

I asked them if I could have detailed data from this study by centre. It had been made available to Wells for the EPA report Appendix, but I had never seen these data. No clear answer emerged but I have raised the point again in a letter to Boffetta.

Although we did not get into the technicalities of misclassification, it was clear that they felt this was an area of potential importance which had not yet been fully resolved. However I also believe they felt that it was only likely to explain a part of the ETS/lung cancer association, and that there was a part that represented a real effect of ETS exposure.

4.9 Future IARC Monographs

They had recently had a meeting to discuss subjects for future IARC monographs. ETS was raised as a possibility but no decision has yet been made. Given the paucity of epidemiological evidence on ETS available at the time of IARC Monograph 38 on Tobacco Smoking, it seems to me quite likely that they will do another sometime, considering only ETS, though maybe they will wait until their multicentre study results are analyzed.

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4.10 Paper by JT, PB, RS and Hirsch (Annex 4)

This was only given to me just before I left and there was no time for discussion. Having read it subsequently I did note the following particular points of interest as regards ETS/lung cancer:

(i) There are statements, "One might expect to find that ... the risk in individuals passively exposed to cigarette smoke may approach the risk found for very light smokers" and "Studies of the concentrations of cotinine in the urine and saliva of passive smokers suggest that the dose received may be equivalent to smoking up to three cigarettes a day" (citing Matsukura et al, 1984), which suggest the authors have totally misinterpreted the likely relative dose that active and passive smokers receive. Matsukura's data have, of course, been long known to be based on erroneous chemistry.

(ii) The results shown in Table 2 show enormous selection bias. Rather than choose an index and give data relevant to it for each study, the authors tend to pull out the largest relative risk they can find. This gives the reader a totally false picture of the strength of the association.

(iii) The paper does not make it clear that the data since 1986 have dramatically reduced the overall meta-analysis relative risk estimate for spouse smoking, from about 1.35 to about 1.17.

(iv) Cross weaknesses in some of the risk assessments cited on p2065 are not even noted (e.g. Kawachi assuming that workplace risks are four times those from spousal exposure!).